Inborn Errors of Metabolism: Amino Acid Metabolism and Neurometabolic Disease

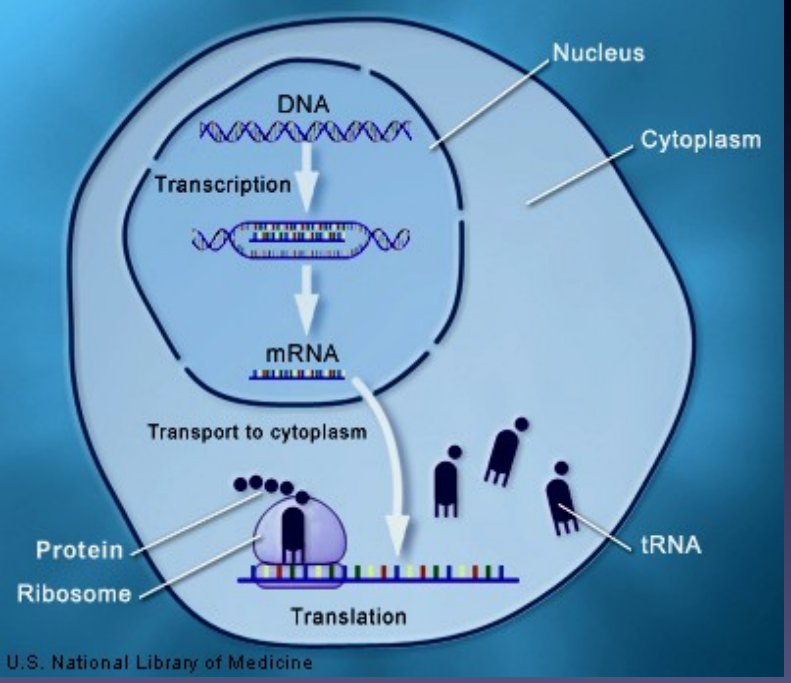
Andrew J Bauer, Pediatric Endocrinology
and
Kathryn Camp, Pediatric Nutritionist

Goals for Today

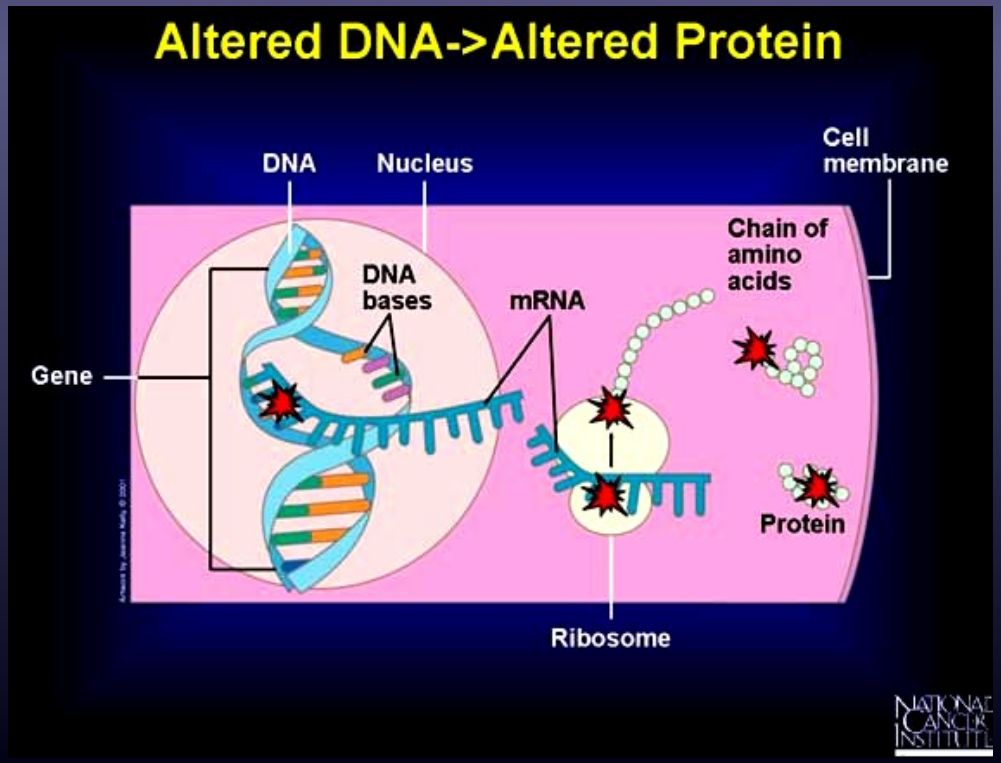
- Provide an appreciation for the complexity and heterogeneity of metabolic disorders
- Provide insight into the lives of several patients and families who deal with these disorders every day
- Provide an appreciation for the complexity of translating “metabolic prescriptions” into real life foods
- Provide the opportunity to “savor” metabolic formula

Generalities of Inherited Disorders

Genetic Basis of Inherited Disorders



Point mutations, Insertions, Deletions, Missense Mutations and Rearrangements



Genetic Basis of Inherited Disorders

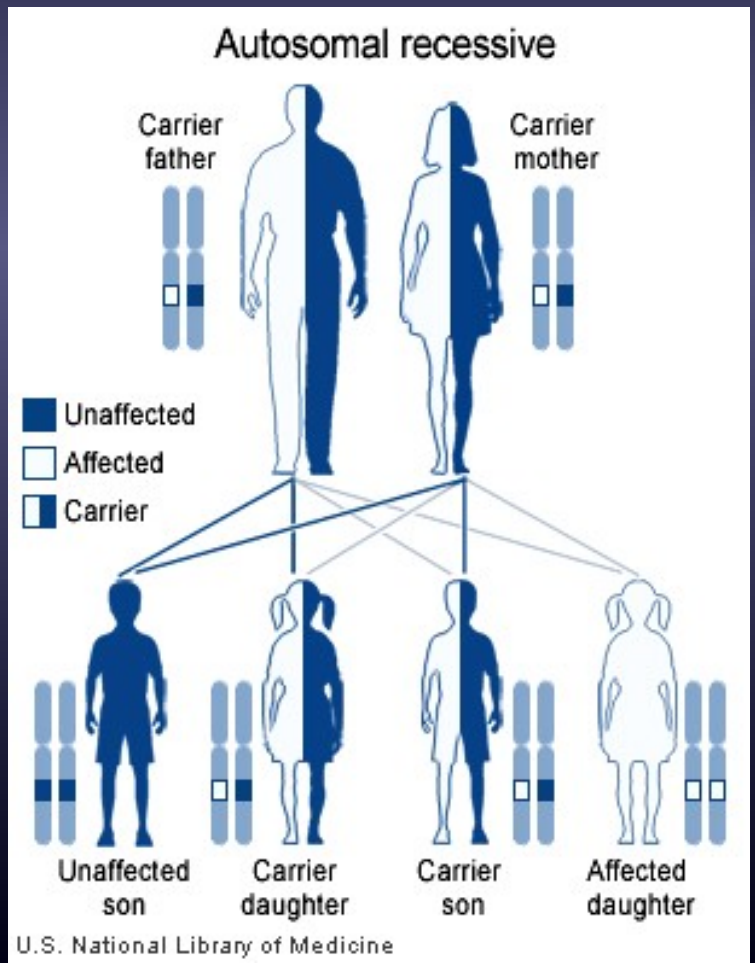
- Depends on the gene – tumor suppressor, oncogene, enzyme (steroid biosynthesis, metabolic pathway)

Gene	Finding
PTEN	Cowden Tumor Syndrome
PRKAR1A	Carney Complex
CYP21	Congenital Adrenal Hyperplasia
PAH	Phenylketonuria

What is the phenotype
(what are the physical features)
Of
Children
With
Inborn Errors of Metabolism ?

Generalities of Inherited Disorders

- Although each individual IEM is rare, cumulatively they occur ~ 1:5000 live births
- Majority of IEM follow an autosomal recessive mode of inheritance



Inborn Errors of Metabolism

- Uneventful delivery
- Normal birth weight
- Non-dysmorphic (no physical findings)
- Uneventful days -> weeks

Syndrome 1

Case 1

- Patrick: 2 yr 4 mo male
- Developmental delay
- Seizures

Patrick

- Birth History: Full Term, 3,620 gm
- Uncomplicated Pregnancy, Labor & Delivery
- Mother 24 yr old, healthy
- No Prenatal exposure to alcohol, drugs, infection, known teratogens
- Discharged home on day of life 2

Case 1 (*CONTINUED*)

Developmental Hx

- Rolled over – 3 months
- Social smile - 4 m
- Jabbered – 9 m
- Stand alone – 14 m
- First word – 18 m
- Phrases – not yet
- Walk alone – 2 yr

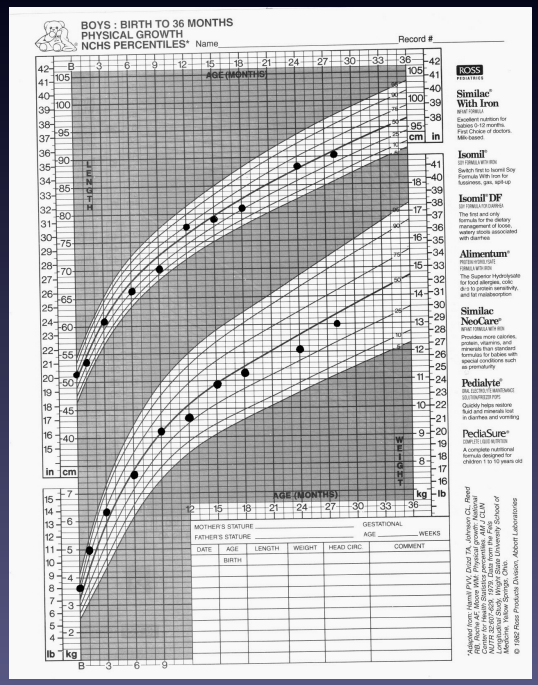
Seizure History

- First – 11 m
- Generalized, tonic/clonic
- Total – 4 seizures
- EEG – diffuse slowing, no focal spike/wave
- MRI – decreased grey/white differentiation and cortical atrophy

Case 1

Anything of note on his physical exam ?

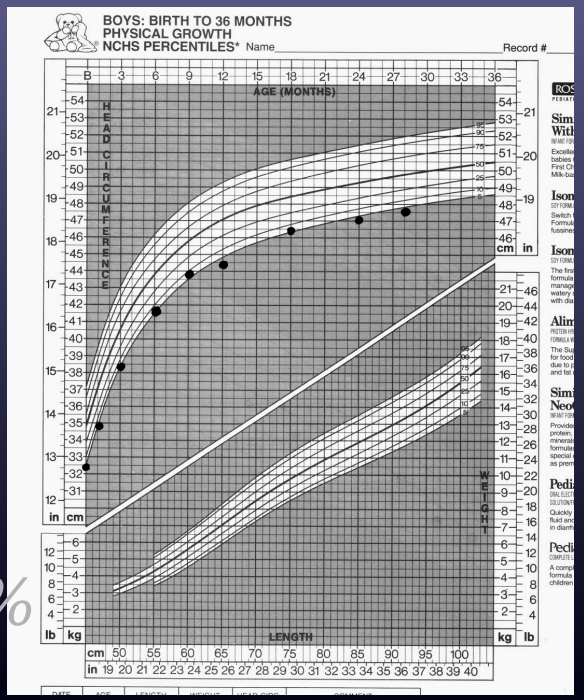
Case 1 (*Cont*)



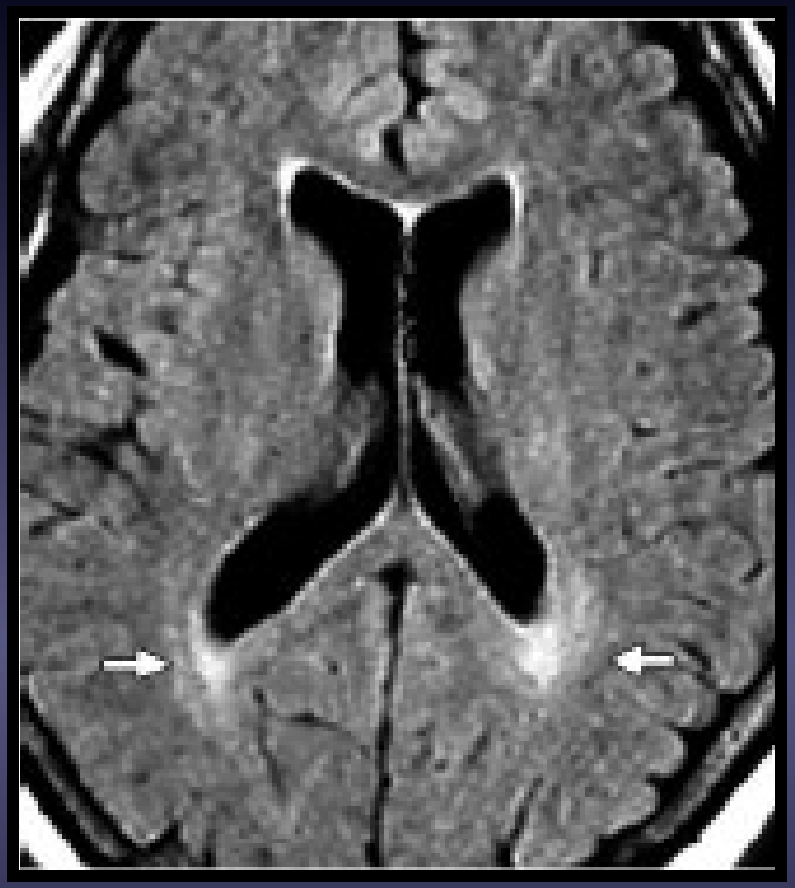
Length 50%
Weight 50%

Physical Exam

- Growth
- Blond hair, blue eyes
- Non-dysmorphic child
- Neurological exam:
  - Decreased tone, brisk reflexes



HC < 5%



Normal **Patrick**

- Abnormal high intensity signal in deep wh
- Leucodystrophy and Cortical atrophy

Case 2

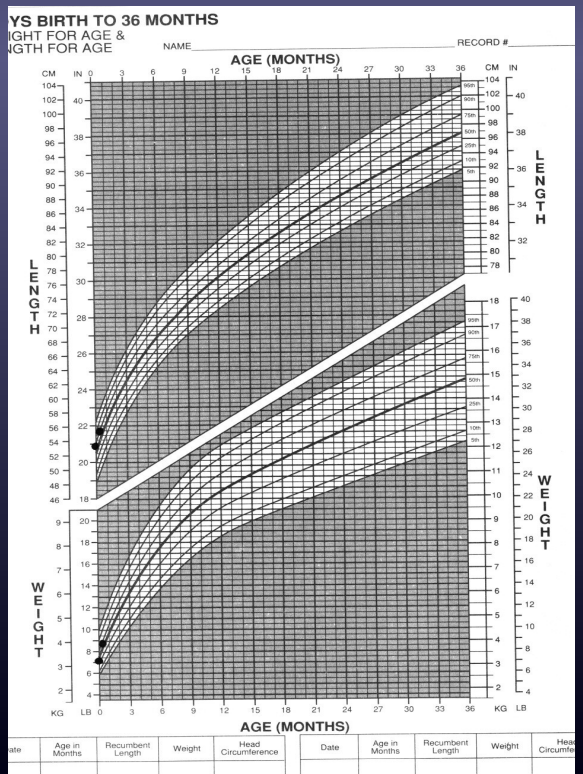
- Jeremy newborn male
- Full Term: 3,100 gm
- Uncomplicated P,L & D
- No perinatal infection, no alcohol, no drugs, no known teratogens

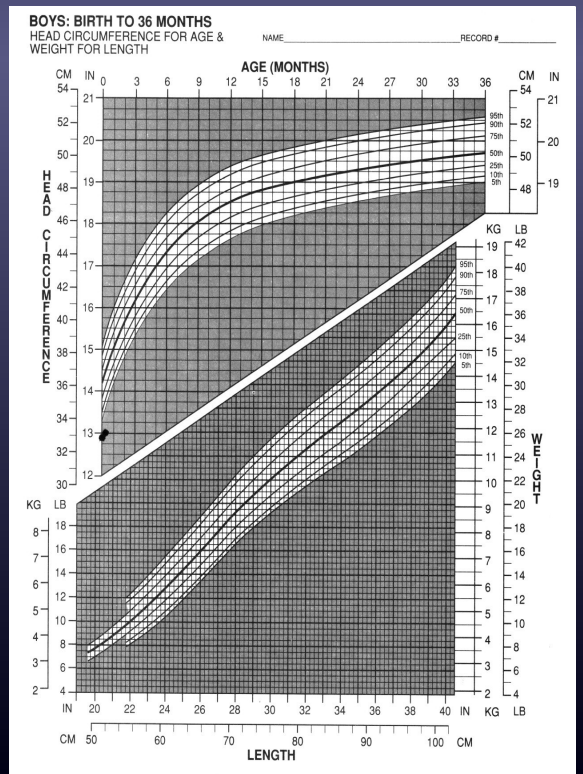
- Mother - 19 yr old
- Functional MR
- No meds
- First Pregnancy

- Father -18 yr old
- Healthy

Case 2
Physical Exam and Labs

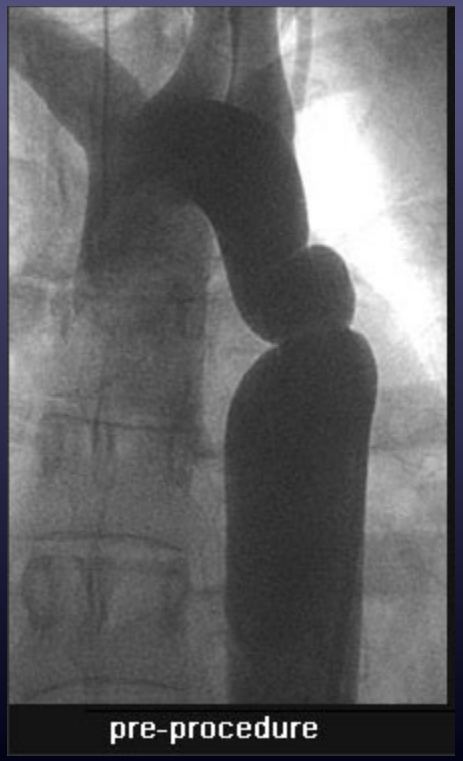
- Ht & Wt = 70% General exam normal
- HC< 5% Neurological exam - normal
- Urine Ferric Chloride ($FeCl_{3)}$ is positive





Case 2

- Jeremy is now 13 years old and exhibits
  - Persistent microcephaly
  - Spasticity
  - Mental retardation
- Coarctation of Aorta, repaired



Case 3

Luis (8yo) referred to Developmental Pediatrics clinic

Chief Complaint: Hyperactivity and Learning Disabilities

Patient and his Brother

- Self selects diet
  - low in meat, eggs, cheese
  - enriched in fruits / vegetable
- Similar pigmentation to his brot

Case 4

- Hannah: 6 month old female
- Diagnosed with metabolic disorder on abnormal newborn metabolic screen
- Normal growth / development
- Normal physical exam
- On treatment with metabolic formula

All four cases

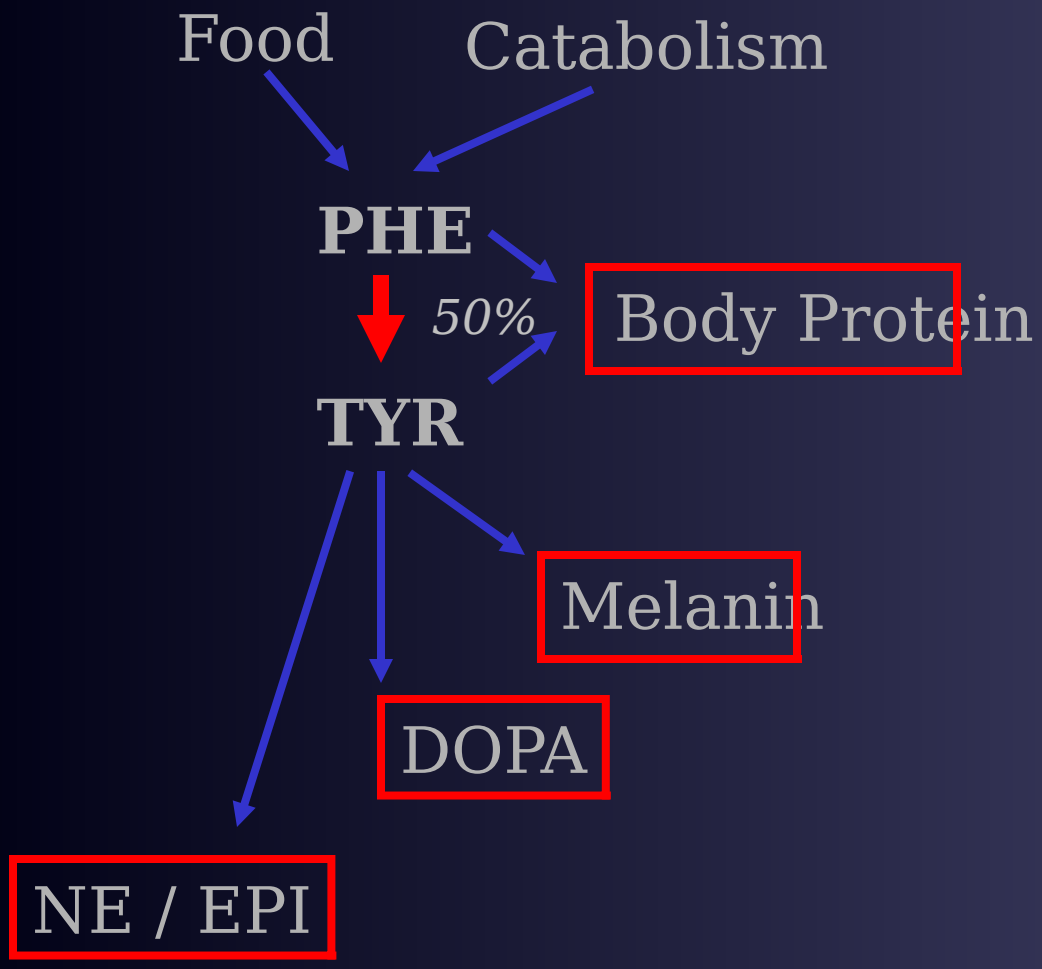
- Examples of hyperphenylalanemia
- Defects in metabolism of phenylalanine
- Prototype – PKU
  - Elevation of PHE > 20 mg/dl
  - Normal < 2 mg/dl
  - Levels 2 –> 20 hyperPHE

PKU

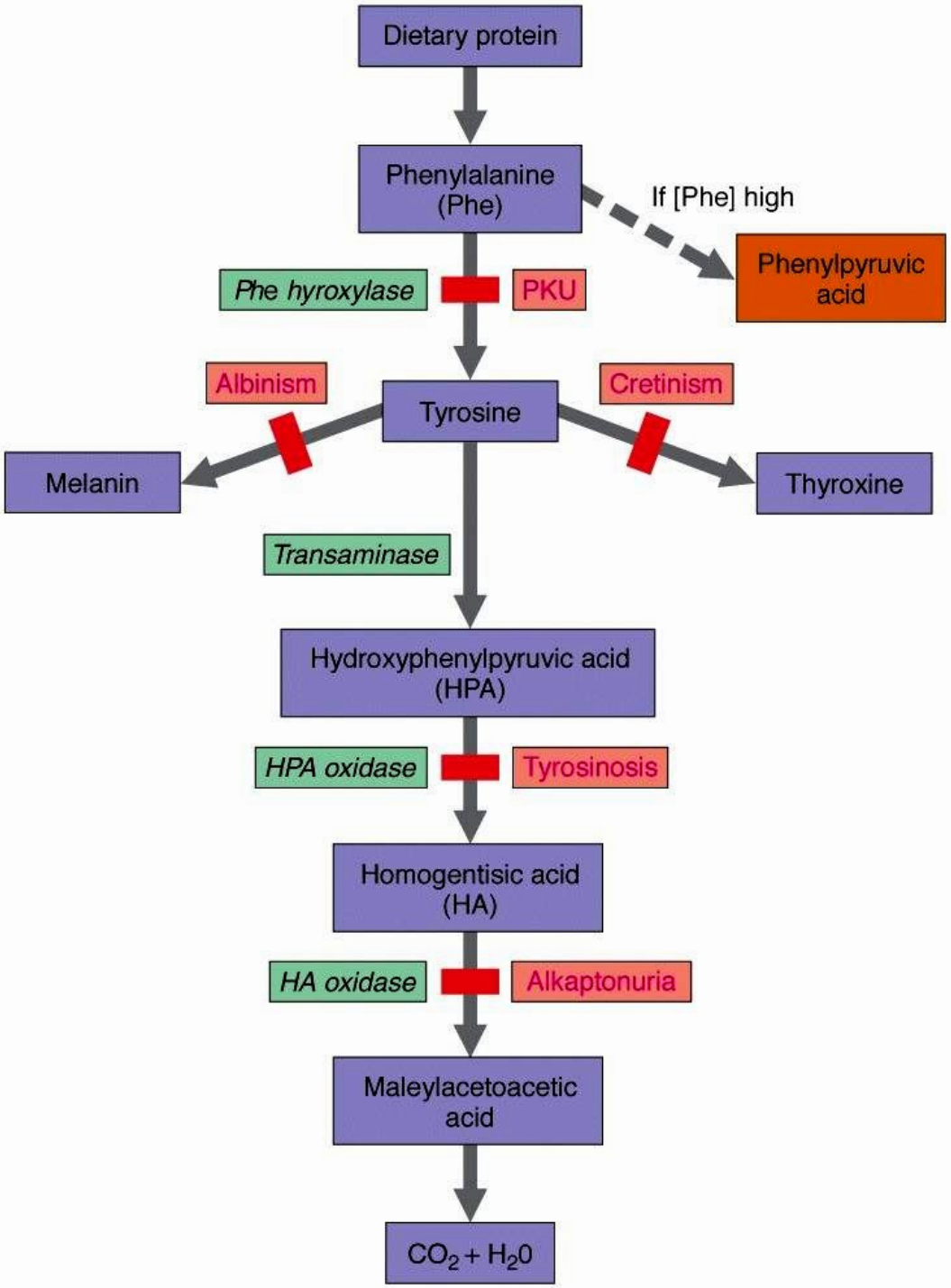
Clinical Findings

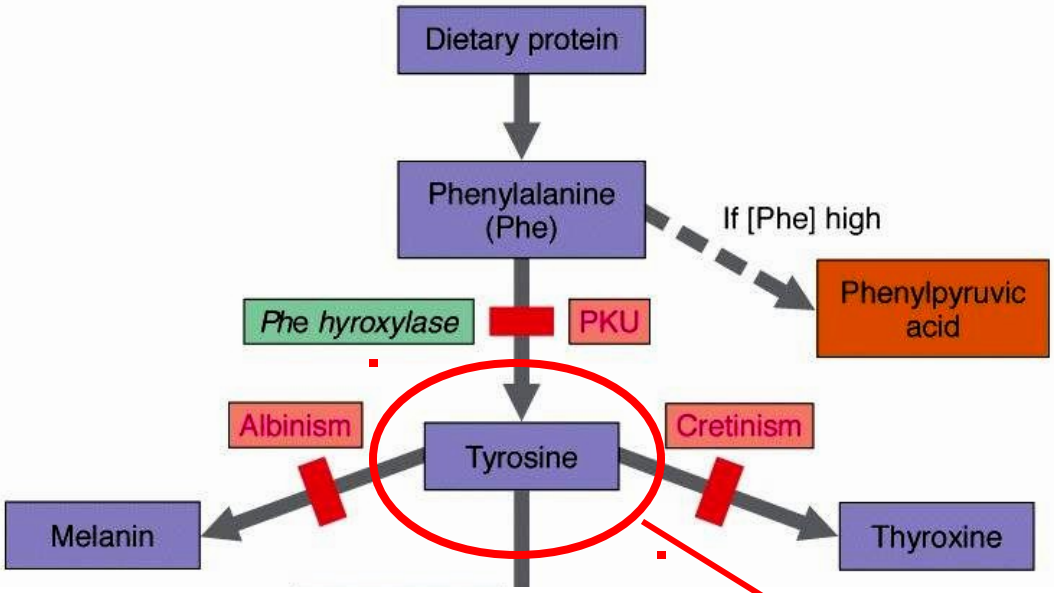
- Mousy or musty odor
- Exzema
- Fair coloring (decreased hair and skin pigmentation)
- Behavior Problems
  - ADHD
- Mental Retardation
  - Lose ~ 1 IQ point per week of non-treatment

Phenylalanine Metabolism



- Phenylalanine
- Essential AA
- Major interconversions through tyrosine

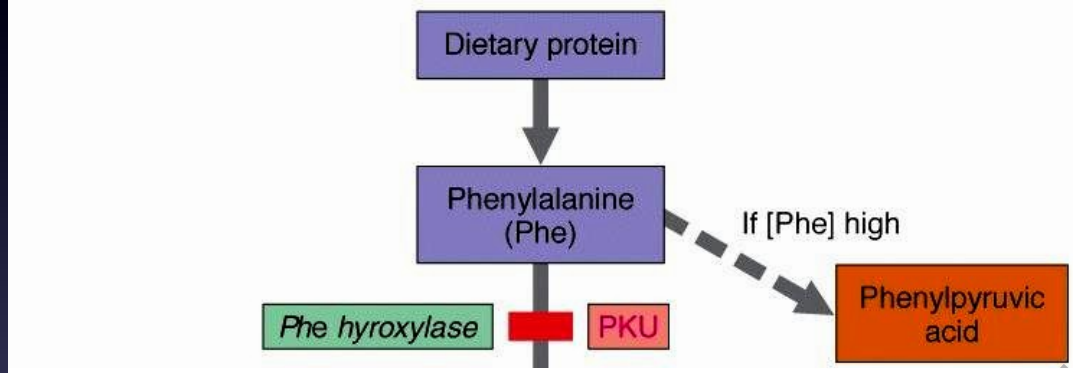

Dietary protein
Phenylalanine (Phe)
If [Phe] high
Phenylpyruvic acid
Phe hyroxylase
PKU
Albinism
Tyrosine
Cretinism
Melanin
Thyroxine
Transaminase
Hydroxyphenylpyruvic acid (HPA)
HPA oxidase
Tyrosinosis
Homogentisic acid (HA)
HA oxidase
Alkaptonuria
Maleylacetoacetic acid
$CO_2 + H_20$



Conditionally Essential AA

Essential Amino Acids

Histidine
Isoleucine
Leucine
Lysine
Methionine (and/or cysteine)
Phenylalanine (and/or tyrosine)
Threonine
Tryptophan
Valine



Urine

Alternate Dispos

Phenyl lactate
Phenylacetate
Phenylethylamine
Phenylacetyl glutami

Mousy or musty odor

PKU

- Autosomal Recessive disorder caused by mutation in *PAH* gene
- Newborn screening started in 1963
- Incidence: 1 in 15,000
- Subtypes and heterogeneity
  - Classic
  - Moderate and mild
  - Non-classical or non-PKU hyperphenylalaninemia

PKU

- Autosomal Recessive disorder caused by mutation in *PAH* gene
- Newborn screening started in 1963
- Incidence: 1 in 15,000
- Subtypes and heterogeneity
  - Classic
  - Moderate and mild
  - Non-classical or non-PKU hyperphenylalaninemia

➔ % enzyme activity determines clinical severity

PKU

- Autosomal Recessive disorder caused by mutation in *PAH* gene
- Newborn screening started in 1963
- Incidence: 1 in 15,000
- Subtypes and heterogeneity
  - Classic
  - Moderate and mild
  - Non-classical or non-PKU hyperphenylalaninemia

➔ % enzyme activity determines clinical severity

PKU

- Autosomal Recessive disorder caused by mutation in *PAH* gene
- Newborn screening started in 1963
- Incidence: 1 in 15,000
- Subtypes and heterogeneity
  - Classic (tolerate < 250mg phe/day)
  - Mild (tolerate 400-600mg phe/day)
  - Hyperphenylalaninemia (normal diet)

➔ % enzyme activity determines clinical severity

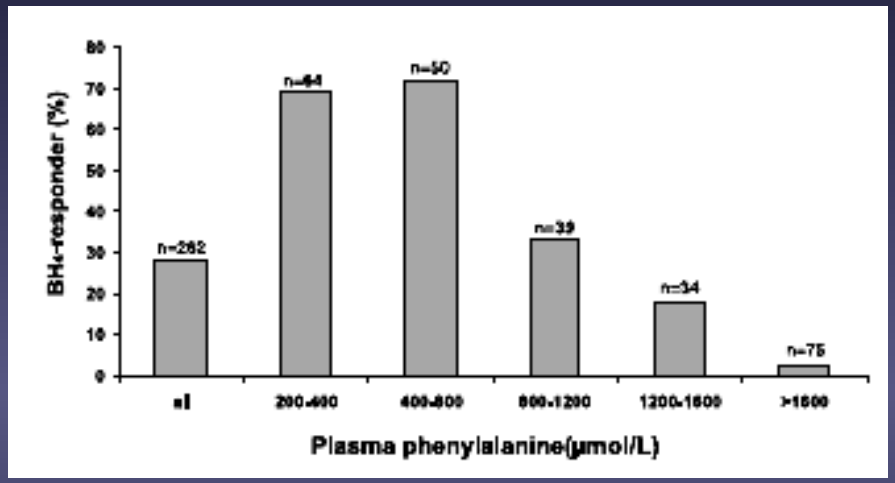
PKU

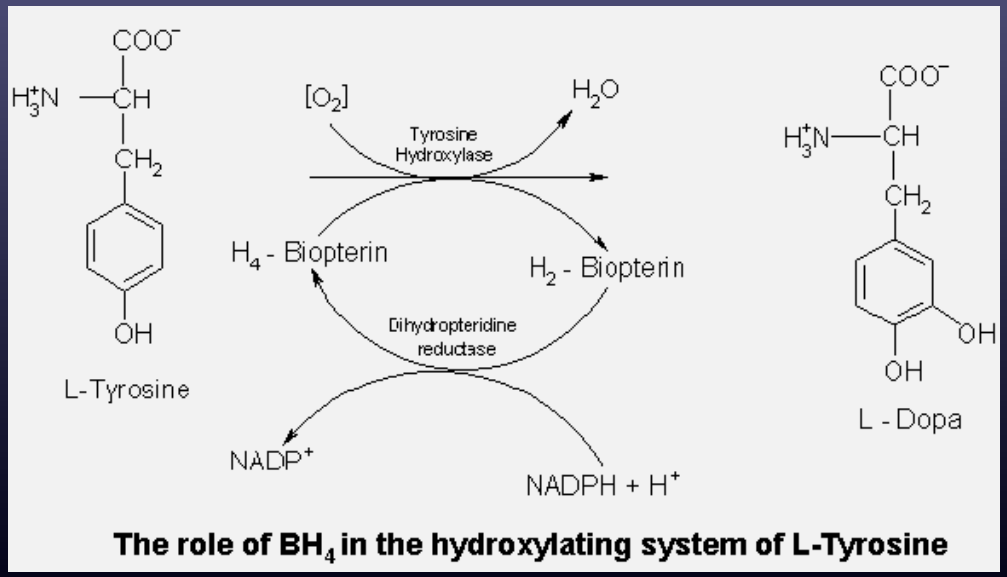
- Autosomal Recessive disorder caused by mutation in *PAH* gene
- Newborn screening started in 1963
- Incidence: 1 in 15,000
- Subtypes and heterogeneity
  - Classic
  - Moderate
  - Mild
  - Hyperphe

Tetrahydrobiopterin (BH4) responsive Hyperphenylalaninemia

- Urine pterins

BH_4 Responders





- *PAH* mutation
  - 62% catalytic
  - 21% regulatory
- Allelic pattern
  - 1 mild + 1 severe
  - 2 mild
  - 2 severe (rare)
- Diet – BH_4 without protein restriction

Biological Effects

- Neurometabolic
  - Critical or vulnerable period in brain development
    - Fetus is protected
    - Birth -> adolescence – linear growth and arborization of cortical neuron dendrites and formation of cortical synapses
  - HyperPhe inhibits transport of large, neutral AA into the brain (as does Leucine)
    - Inhibition of protein and neurotransmitters

    ➔ Deficiencies of dopamine, serotonin

Major Neuropathologic changes

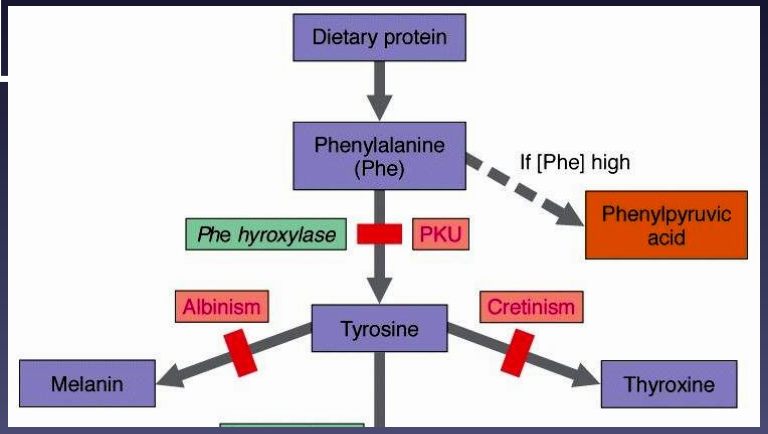
1. Hypomyelination (Phe-sensitive oligodendrocytes)
2. White matter degeneration (leucodystrophy)
   - Lifelong risk
3. Developmental delay/arrest cerebral cortex

➔ Microcephaly
➔ Mental retardation
➔ Seizures

Non-Neuro pathology

- Hypomelanosis – Why ?

Non-Neuro pathol



- Hypomelanosis
  - Blond hair, blue eyes, pale
  - Deficient Tyrosine production (precursor of Melanin)
- Cardiac
  - Coarctation of the Aorta
  - Hypoplastic left heart
  - Tetralogy of Fallot

Maternal PKU syndrome

- First mentioned in literature in 1937
- First mentioned as a complication of PKU in 1956
  - Women with MR and PKU has 3 children, all retarded despite not having PKU
- Microcephaly and cardiac defects reported in 1960’s
- 1983 – MPKUCS begun

Maternal PKU Collaborative Study

- Untreated women
  - 92% risk of mental retardation
  - 73% risk of microcephaly
  - 40% risk of low birth weight
  - 12% risk of congenital heart disease
    - Unknown why 85% are not effected
    - Reduced risk if maternal plasma phe levels are normalized pre-conceptually

Maternal PKU syndrome

- Dose-Response Relationship
  - Goal: Phe level between 2-6 mg/dl by 8 weeks

Table 2. *Frequencies of at-risk mothers with treated maternal PKU* who bore offspring with CHD, categorized by APL*

	APL (μM)			
Mothers	900–1200	1201–1500	1501–1800	1801–3000
Total number	30	46	49	51
% with CHD offspring (*n*)	13% (4)	7% (3)	18% (9)	33% (17)†

* APL ≥ 900 μM and not in metabolic control by the eighth gestational week.

The longer it takes to get Phe level < 8 mg/dl the lower the IQ of the baby

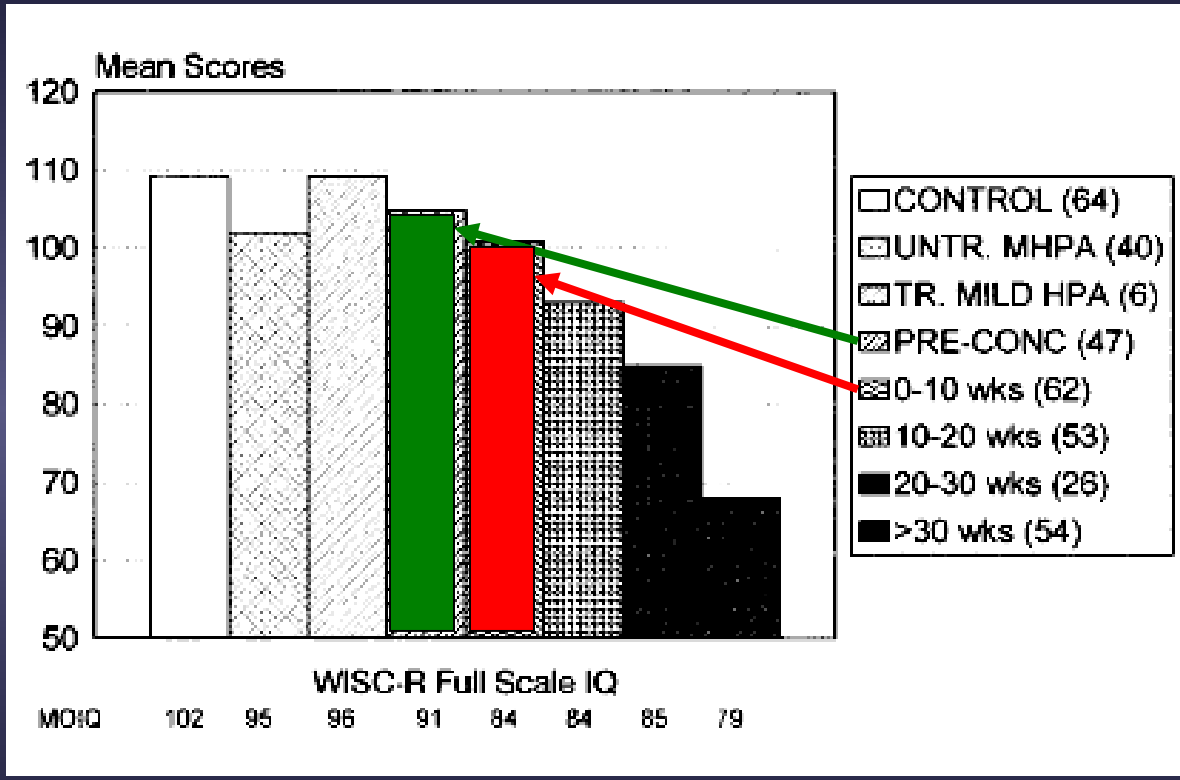
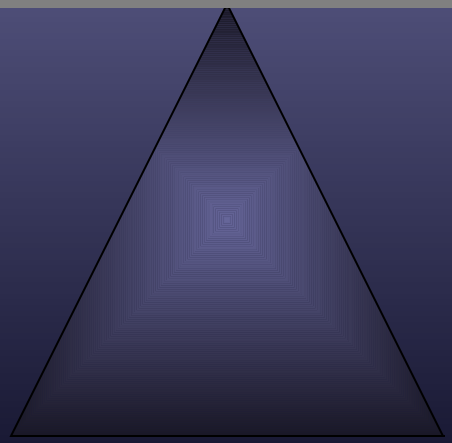


Fig 5. Seven-year WISC-R scores of offspring of HPA and control women by gestational age at which maternal blood Phe <600 µmol/L was achieved.

Balancing Metabolic Control

Exposure to **normal** PHE intake

Elimination of PHE from the diet



Balancing Metabolic Control

- Exposure to **normal** PHE intake:
  - Elevations of PHE
  - Elevations of PHE-ketones
  - Deficient TYR, DOPA, NE, EPI
  - Mental retardation / seizures

Balancing Metabolic Control

- Exposure to **normal** PHE intake:
  - Elevations of PHE
  - Elevations of PHE-ketones
  - Deficient TYR, DOPA, NE, EPI
  - Mental retardation / seizures

=
Bad

Balancing Metabolic Control

- **Elimination** of PHE from the diet:
  - Decreases PHE
  - Decreases PHE-ketones
  - Deficient TYR, DOPA, NE, EPI
  - **DEATH** from essential AA deficiency

Balancing Metabolic Control

Bad =

- **Elimination** of PHE from the diet:
  - Decreases PHE
  - Decreases PHE-ketones
  - Deficient TYR, DOPA, NE, EPI
  - **DEATH** from essential AA deficiency

Optimal Therapy of PKU

- Initiate treatment by 7 days of life
- Phenylalanine levels

Age	Level	Freq of Testing
0-12 months	2-6 mg/dl	1x/week
1-12 years	Same	2x/month
> 12 years	2-15 mg/dl	1x/month
Pregnancy	2-6 mg/dl*	2x/week

** 3m before conception*

Lifelong Treatment

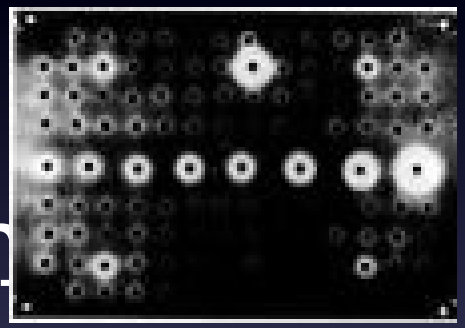
- Acute illness or Surgery
  - Endogenous Phe production during catabolic state
- Adult
  - Stable IQ
  - Poor performance of attention and speed of processing

What have we learned ?

- Hyperphenylalanemia
  - An abnormal lab finding
  - Several defects may result in hyperphe
- Specific Dx is critical
  - PHE restriction in BH_4 deficiency is lethal

- Treatment is
  - Effective if begun early and continued for life
  - Abnormal MRI develops when patients stop Rx
  - Aggressive management during growth and during illness

Newborn Screenin



- Newborn Screening - misses about 10% of all cases
  - Guthrie Bacterial Inhibition Assay
    - 1961 developed filter paper assay (Buffalo, NY)
    - Bacillus subtilis – PHE required for growth, absent from media
  - Fuorometric Analysis
  - Tandem Mass Spectrometry
    - Few false positives
    - Can simultaneously obtain Tyrosine levels

Disorders Included in th StepOneTM Newborn Screening Panel

http://www.pediatrix.c

DISORDERS DETECTED BY TANDEM MASS SPECTROMETRY

ACYLCARNITINE PROFILE

Fatty Acid Oxidation Disorders

Carnitine/Acylcarnitine Translocase Deficiency
Carnitine Palmitoyl Transferase Deficiency Type I[1]
3-Hydroxy Long Chain Acyl-CoA Dehydrogenase Deficiency
2,4-Dienoyl-CoA Reductase Deficiency[1]
Medium Chain Acyl-CoA Dehydrogenase Deficiency
Multiple Acyl-CoA Dehydrogenase Deficiency
Neonatal Carnitine Palmitoyl Transferase Deficiency Type II
Short Chain Acyl-CoA Dehydrogenase Deficiency
Short Chain Hydroxy Acyl-CoA Dehydrogenase Deficiency
Trifunctional Protein Deficiency
Very Long Chain Acyl-CoA Dehydrogenase Deficiency

Organic Acid Disorders

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency
Glutaric Acidemia Type I
Isobutyryl-CoA Dehydrogenase Deficiency
Isovaleric Acidemia
2-Methylbutryl-CoA Dehydrogenase Deficiency
3-Methylcrotonyl-CoA Carboxylase Deficiency
3-Methylglutaconyl-CoA Hydratase Deficiency
Methylmalonic Acidemias
- Methylmalonyl-CoA Mutase Deficiency
- Some Adenosylcobalamin Synthesis Defects
- Maternal Vitamin B12 Deficiency

Mitochondrial Acetoacetyl-CoA Thiolase Deficiency
Propionic Acidemia
Multiple-CoA Carboxylase Deficiency
Malonic Aciduria

AMINO ACID PROFILE

Amino Acid Disorders

Argininemia
Argininosuccinic Aciduria
5-Oxoprolinuria[1]
Carbamoylphosphate Synthetase Deficiency[1]
Citrullinemia
Homocystinuria
Hypermethioninemia
Hyperammonemia, Hyperornithinemia, Homocitrullinemia Syndrome[1]
Hyperornithinemia with Gyral Atrophy1
Maple Syrup Urine Disease
Phenylketonuria
- Classical/Hyperphenylalaninemia
- Biopterin Cofactor Deficiencies

Tyrosine
- Transient Neonatal Tyrosinemia
- Tyrosinemia Type I[1]
- Tyrosinemia Type II
- Tyrosimenia Type III

Other

Hyperalimentation
Liver Disease
Medium Chain Triglyceride Oil Administration
Presence of EDTA Antigoagulants in blood specimen
Treatment with Benzoate, Pyvalic Acid, or Valproic Acid
Carnitine Uptake Deficiency[1]

Disorders Detected by Other Technologies

Biotinidase Deficiency
- Complete Deficiency
- Partial Deficiency

Congenital Adrenal Hyperplasia
- Salt Wasting 21-Hydroxylase Deficiency
- Simple Virilizing 21-Hydroxylase Deficiency

Congenital Hypothyroidism
(not valid after 2 months of age)

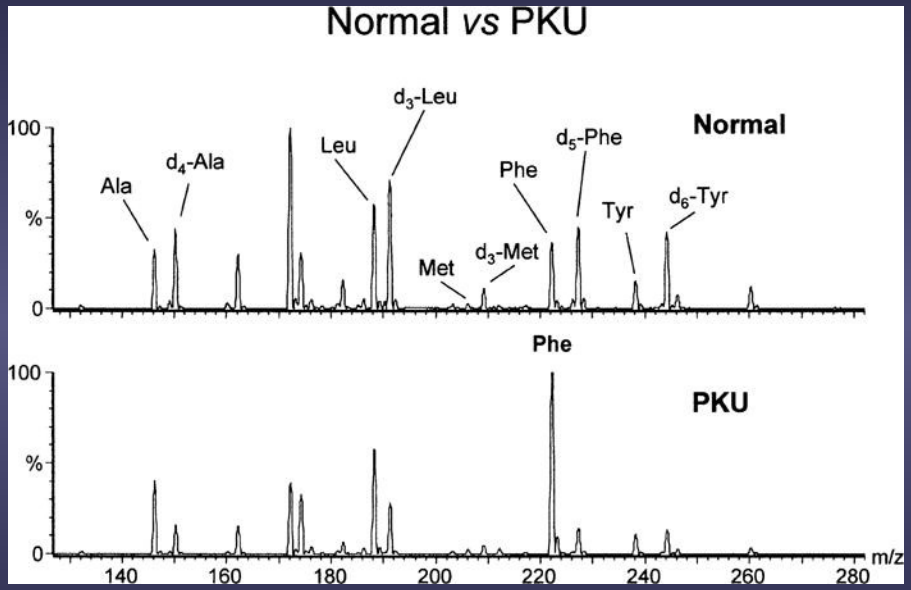
Cystic Fibrosis (not valid after 3 months of age)*

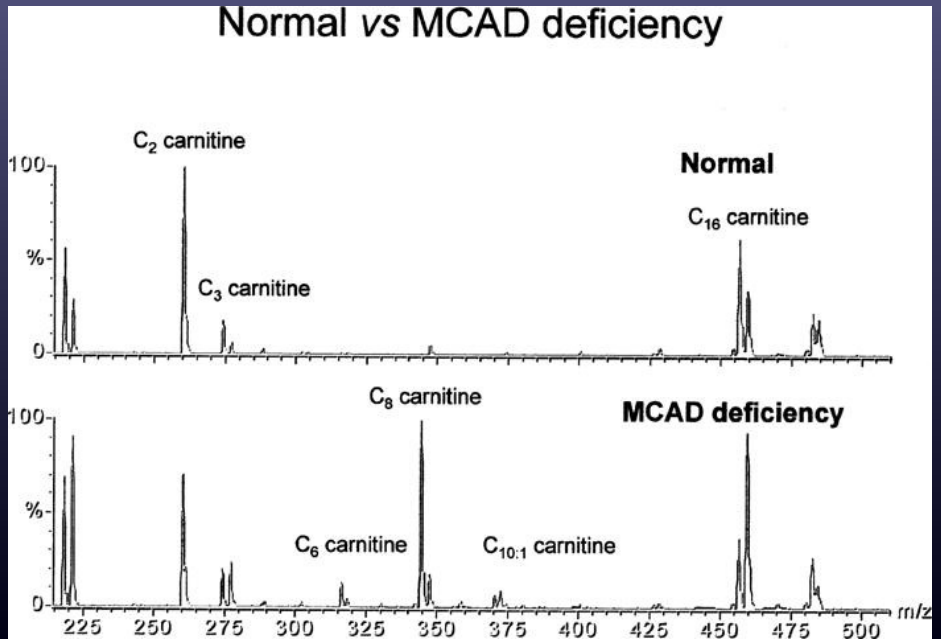
Galactosemia
- Galactokinase Deficiency
- Galactose-1-Phosphate Uridyltransferase Deficiency
- Galactose-4-Empimerase Deficiency

Glucose-6-Phosphate Dehydrogenase Deficiency

Sickle Cell & other Hemoglobinopathies
- Hemoglobin S, S/C, S/Beta-Thalassemia, C, & E Diseases

MS/MS Profiles





What about our cases??

Patrick – case 1

➔ Dx ?

- 3 yr old with developmental delay and seizures…..

Jeremy – case 2

➔ Dx ?

- Newborn with microcephaly and + $FeCl_3$
- Now mentally retarded

Choices

1. Classic PKU – treated or untreated
2. Maternal PKU
3. Hyperphe

What about our cases??

Patrick – case 1

➔ Classic PKU (mod)

- 3 yr old with developmental delay and seizures…..
- Pediatrician failed to do metabolic studies because “newborn screen was normal”
- Patrick has permanent disabilities

Jeremy – case 2

➔ Maternal PKU syndrome

- Newborn with microcephaly and + $FeCl_3$
- Now mentally retarded
- He is metabolically normal… but his mother had PKU
- His mother wants more children but is not on diet

Our Cases

Luis - Case 3

➔Dx ?

- 8yo with learning disability and hyperactivity

Hannah - Case 4

➔ Dx ?

- 6 month old
- Normal growth and development

Choices

1. Classic PKU – treated or untreated
2. Maternal PKU
3. Hyperphe

Our Cases

Luis - Case 3

➔ Classic PKU (Mexico)

- On treatment
- His hyperactivity has improved
- He will not regain normal intellect

Hannah - Case 4

➔ Classic PKU, treated

- Continues to do well on therapy
- Growth, development and intellectual milestones are normal

Syndrome 2

Jakob

- Jakob was the product of a full term pregnancy
- Appeared healthy until day of life nine
  - Hospitalized in ICU
- At 9 months Jakob is developmentally normal and growing well
- However, whenever he has a mild URI, his amino acid levels are dramatically elevated.

- What is MSUD ?
- What odor was the physician asking mom about ?
  - Where else can you smell it ?
  - Is odor a reliable physical finding ?
- What causes neurotoxicity ?
- What is the long-term treatment and outcome ?

MSUD

- Autosomal Recessive
- Mutations in branched chain α-ketoacid dehydrogenase (BCKDH)
  - Mitochondrial enzyme complex
  - 3 subunits (E1, E2, and E3) encoded by 4 unlinked genes

    E1 decarboxylase – heterotetramer (α and β subunits)
    E2 transacylase
    E3 dehydrogenase

➔ E1 is <u>thiamine</u> dependent

Types of MSUD

Type	Clinical	Biochem	Enzyme activity
Classic	neonatal onset	BCAA, BCKA	0-2 %
Intermediate	FTT, develop delay	BCAA, BCKA	3-30
Intermittent	Normal Growth and development	BCAA, BCKA when ill/stressed	5-20
Thiamine responsive*	Similar to Inter	BCAA and BCKA decrease w/thiamine	2-40

Maple Syrup Urine Disease

- Classical
  - Normal newborn, hours to days
  - Poor feeding and drowsiness
  - Critical deterioration with metabolic acidosis, hypoglycemia, cerebral edema, respiratory distress, hiccups, apnea, bradycardia, hypothermia, coma
  - Generalized hypertonic episodes, with opisthotonus (arching), boxing or pedalling

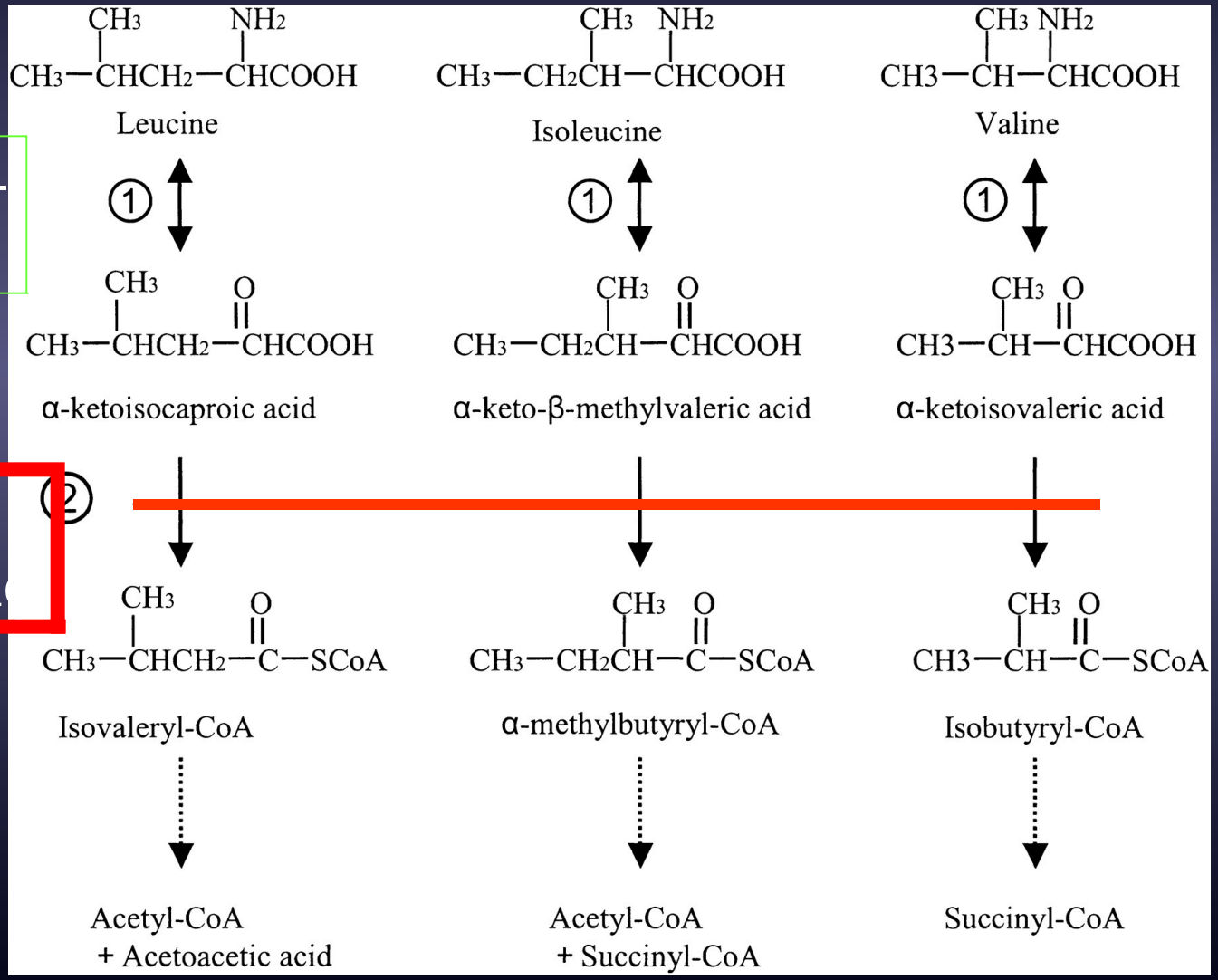
Clinical Manifestations

Time	Symptom/Sign
12-24 hours	Maple syrup odor to cerumen
	Elevated BCAA
2-3 days	Irritability, poor feeding
	Ketonuria
4-5 days	Encephalopathy (lethargy, apnea, atypical movements
7-10 days	Coma and respiratory failure

Metabolic Defect

BCAA amino-transferases

BCKDH
- Rate limitin



Branch Chain Amino Acids

- Leucine, Isoleucine and Valine
- Comprise ~40% of essential AA
- During fasting, ~ 80% of AA released is recycled back into protein synthesis

Branch Chain Amino Acids

- Transamination and oxidative disposal of leucine occurs in skeletal muscle (50%), kidney (25%) and gut/liver (25%)
  ➔Nitrogen released is used to form glutamate -> alanine -> glucose (alanine aminotransferase reaction)

Leucine + α-Ketoglutarate -> α-Ketoisocaproate and Glutamate
Glutamate and Pyruvate -> α-Ketoglutarate and Alanine
Alanine -> -> -> Glucose

Branch Chain Amino Acids

- Increase in supply from diet or proteolysis must be met with appropriate increase in anabolic pathway (blocked in disorder)
  - Most severe biochemical intoxication caused by catabolism of endogenous protein
  - Otitis Media = most common cause of metabolic decompensation

Branch Chain Amino Acids

- Defect leads to elevated levels, more pronounced in infants and children due to enhanced rates of growth
- **Leucine** accumulation is most toxic

Signs/Symptoms of Acute Toxicity

- Ataxia (unsteady, clumsy movements)
- Acute dystonia (involuntary muscle contractions)
- Mood swings
- Nausea, Vomiting, and Anorexia
- Hallucinations
- Altered level of consciousness
- Stroke, coma, and death

Signs/Symptoms of Chronic Toxicity

- ADHD
- Mood Disorders – anxiety and depression
- Mental retardation
- Neurologic deficits (stroke)

Neurotoxicity of Leucine

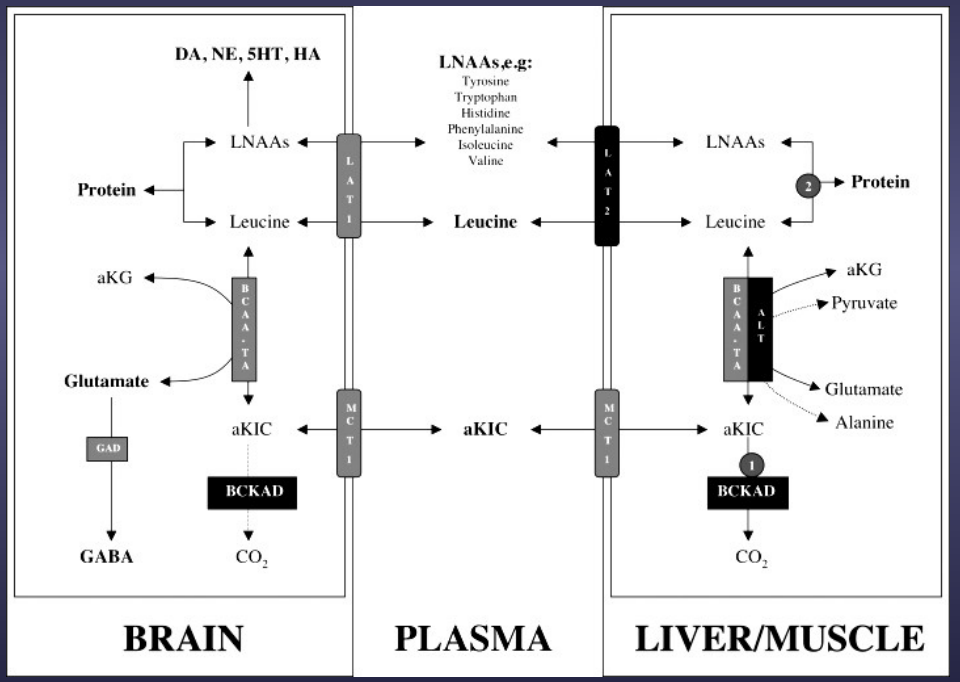
1. Leucine and KIC intracellular accumulation results in cellular edema

Neurotoxicity of Leucine

1. Leucine and KIC intracellular accumulation results in cellular edema
2. Leucine accumulation inhibits entry of other large neutral amino acids

Neurotoxicity of Leucine

1. Leucine and KIC intracellular accumulation results in cellular edema
2. Leucine accumulation inhibits entry of other large neutral amino acids



➔ Disrupted monoamine transmitter production

➔ Decreased ‘fast’ neurotransmitter pools – glutamate, GABA, aspartate

Neurotoxicity of Leucine

1. Leucine and KIC intracellular accumulation results in cellular edema
2. Leucine accumulation inhibits entry of other large neutral amino acids
3. Metabolites (KIC) induce oxidative injury

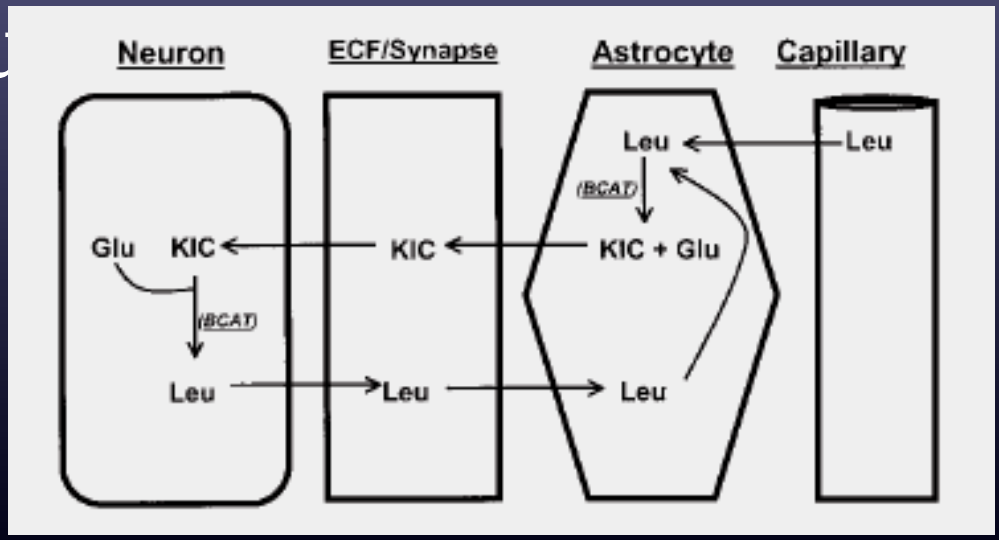
➔ Melatonin, Vitamins C and Emay be protective

Neurotoxicity of Leucine

1. Leucine and KIC intracellular accumulation results in cellular edema
2. Leucine accumulation inhibits entry of other large neutral amino acids
3. Metabolites (KIC) induce oxidative injury
4. Excess KIC results in consumption of substrates needed for malate-aspartate shuttle resulting in increased brain lactate and energy failure

Neurotoxicity of Leucine

- Glutamic Acid is a crucial excitatory neurotransmitter
- Leucine is trafficked to the brain as a source of $-NH_2$ groups (Leucine-Glu



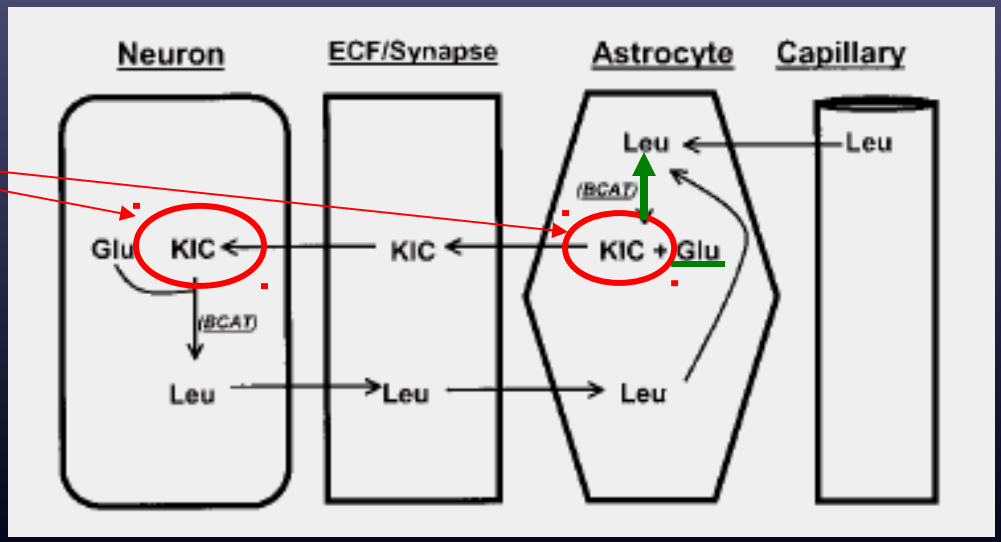
Neurotoxicity of Leucine

- Elevated Leucine
  - Accumulation of KIC drives leucine-glutamate cycle in reverse direction -> decreased brain glutamate

LEU

2-ketoisocaproate

Isovaleryl-CoA



Neurotoxicity of Leucine

KIC + glutamate -> Leucine + α-Ketoglutarate

-> increased Aspartate utilization

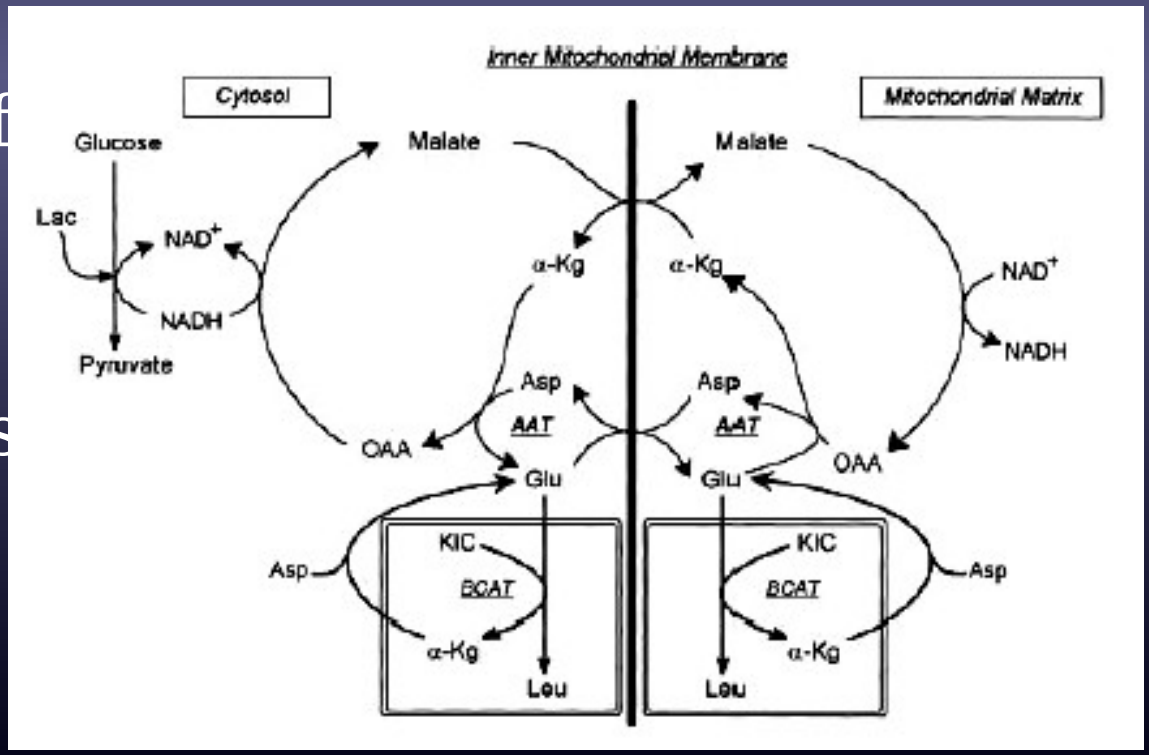
-> decreased functioning of malate-aspartate shuttle

-> Decreased transf

of reducing equiv

-> energy failure

and lactic acidosis



Neurotoxicity of Leucine

- Elevated Leucine
  - – Altered brain water homeostasis -> cell edema
  - ➔ Inhibits entry into the brain of other large, neutral AA (as in PKU)
  - - phenylalanine, tryptophane, methionine, tyrosine, histidine, threonine, and BCAA (L1-NAA-t)
  - - Dystonia and ataxia may arise from acute deficiency of tyrosine and dopamine
  - - Decreased dendritic branching, hypomyelination

MSUD
Goals of Treatment

- Restriction of Leucine, Isoleucine, and Valine to maintain post-prandial plasma BCAA near normal level
  - Supplement free valine and isoleucine

MSUD
Acute Treatment

- Treat precipitating event
- Give 1.5-3.0 times the estimated energy requirement with 40-50% as lipid
  - Age dependent (based on body weight or SA)
  - May need to add insulin
- Provide BCAA-free essential and non-essential amino acids
- Give glutamine and alanine
- Hemodialysis

MSUD
Goals of Treatment

- Excessive restriction*
  - Growth failure
  - Anemia
  - Breakdown of mucosa
  - Immunodeficiency
  - Dysmyelination, abnormal dendritic branching, microcephaly and mental retardation

* May be 2° to prolonged dietary restrictions from acute illness

Impact of dietary Tx

33yr old female

- dx in 1967
- Hospitalized x 6 months at time of dx
- Semi-comatose with frequent seizures
- Fully dependent on facilitated care

Niece

- Dx at 14 *hours* of age
- Asymptomatic
- Born at home
- 6 yrs of age – no hospitalizations and normal growth and development

Follow-Up Jacob – Age 4 yr

- Family unwilling to tolerate
  - Continual stress of life threatening disorder
  - Rigors of dietary management (weighing all foods, forcing feeds by G-tube when not interested in eating)
  - Severe limitations on their lives

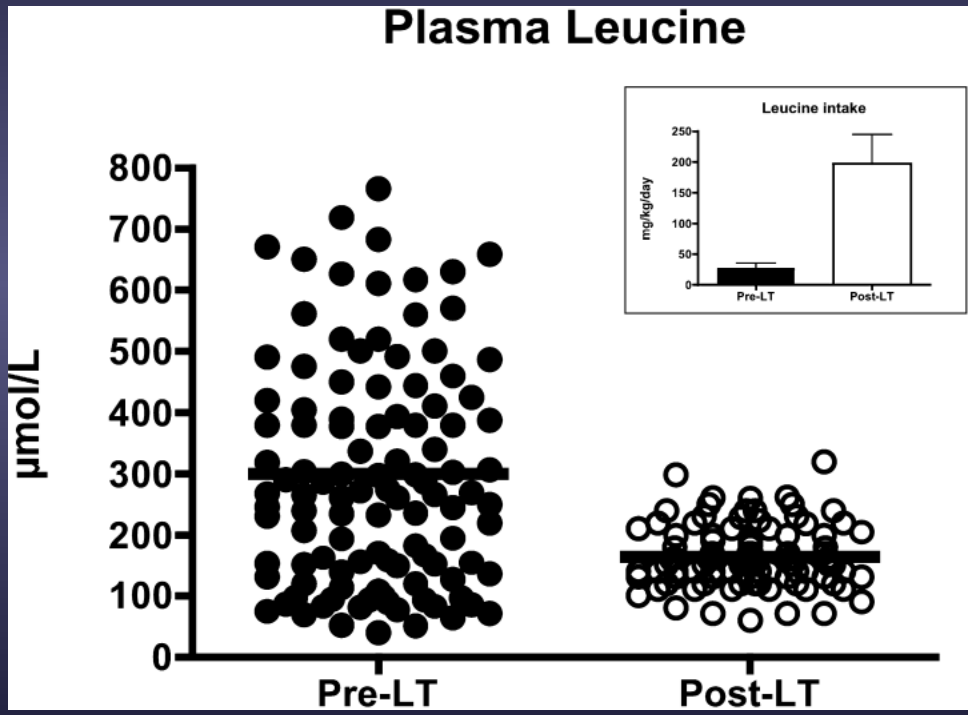
Liver Transplantation

Liver Transplantation

- Liver transplantation results in increase in whole body BCKD activity
  - Muscle = 50%
  - Kidney = 25%
  - Liver and gut = 25%
- Placed on liver transplant list at Pittsburgh and underwent successful liver transplant 3 years ago
- Now on unrestricted diet

Liver Transplant: Outcomes

- Normalization of BCAA within 6-12 hours
- Sustained normalization of BCAA on unrestricted diet (4-18 months f/u)



Strauss KA. Am J Transpl;

Cost

- Quality of life
- Money

MSUD Med Tx	Liver Trans and f/u
$ 7000-10,000/year	$ 300-400,000 initial
+	
$ 10-20,000/year f/u	

Take home points

Suspect a neurometabolic disorder if

- Normal newborn -> neurologic decompensation with
  - Metabolic acidosis
  - Ketonuria
- Developmental delay or Mental retardation
- Seizures
- Unexplained death
- Unusual odor

Take home points

- Ketonuria in a newborn should always be considered pathologic
- Newborn screening may miss diagnoses
  - Plasma amino acid and urine organic acid analysis must be sent emergently
  - Tandem mass spectrometry avoids false negative rate and speeds screening process

Take Home Points

- A number of metabolic diseases are associated with mutations that respond to cofactors therapy (alter K_m of the enzyme)
  - PKU and biopterin (BH_4)
  - MSUD and thiamine (B1)
  - Homocystinuria and pyridoxine (B6)
  - Methylmalonic aciduria and cobalamin (B12)

Take home points

- Lifelong dietary management with need to ensure absolute patient-provider communication
  - Brain injury commonly occurs 2º to inadequate treatment during intercurrent illness
  - Adults with PKU may not experience medical decompensation but will experience decreased cognitive ability
- Acute or chronic essential amino acid deficiencies result in significant morbidity

Take home points

- Increasing # of women with PKU, MSUD and other metabolic diseases that are having children
- Maintaining control of the disease has significant impact on the mom’s health as well as the infants